PATENT
Docket No. 2026-4202US4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Frank CUTTITTA et al.	
Serial No.	:	Divisional of 09/011,922	Art Unit: To Be Assigned
Filed	:	Herewith (August 16, 2001)	Examiner: To Be Assigned
For	:	**Functional Role of Adrenomedullin (AM) and the Gene-Related Product (PAMP) in Human Pathology and Physiology**	

Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Dear Sir:

Preliminary to the examination of the above-identified divisional patent application, entry and consideration of this amendment are respectfully requested.

IN THE SPECIFICATION:

Please amend the specification by replacing/rewriting the paragraphs as indicated.

At page 3, please replace/rewrite paragraph 2 from lines 16-35, as follows:

(Amended)

AM's role as a vasodilatory agent has been extensively studied (C. Nuki et al., Biochem. Biophys. Res. Commun. 196, 245 (1993); Q. Hao et al., Life Sci. 54, 265 (1994); D. Y. Cheng et al., Life Sci., 55, 251 (1994); C. J. Feng, B. Kang, A. D. Kaye, P. J. Kadowitz, B. D. Nossaman, Life Sci., 433 (1994)). It acts through specific receptors in the plasma membrane to activate adenylate cyclase activity and modulate

Ca^{2}+ flux in the target cells (S. Eguchi et al., Endocrinology 135, 2454 (1994); Y. Shimekake et al., J. Biol. Chem. 270, 4412 (1995)). These signal transduction pathways are involved in numerous physiological processes, including the regulation of hormone secretion. It is well established that regulation of intracellular cAMP modulates hormone release in the pancreas (Y. Korman, S. J. Bhathena, N. R. Voyles, H. K. Oie, L. Recant, Diabetes 34, 717 (1985); C. B. Wollheim, Diabetes 29, 74 (1980)). AM has also been reported to have an effect on Na^{+} channel activity (EP Application No. 0 622 458 A2). Since AM has been reported to influence the secretion rate of several hormones, including catecholamine (F. Kato et al., J. Neurochem. 64, 459 (1995); EP Application No. 0 622 458 A2), adrenocorticotropin (W. K.

At page 8, please replace/rewrite paragraph 2 describing "Figure 8", from lines 16-24, as follows:

(Amended)

Figures 8A and 8B: Characterization of AM by RT-PCR in mRNA from normal tissues and pulmonary tumor cell lines. The PCR products had the proper size (410bp) when visualized with UV light (Figure 8B), and they hybridized with the specific probe after Southern blot (Figure 8A). H146 and H345 are small cell carcinomas, H676 is an adenocarcinoma, H720 is a carcinoid, and H820 is a bronchioalveolar carcinoma. H146 was the only cell line that tested negative for AM.

At page 12, please replace/rewrite paragraph 3 from lines 6-10 as follows:

(Amended)

Figures 25A and 25B: Figures 25A and 25B set forth the distribution of amphipathic regions for AM and PAMP as calculated for a-helix/b-sheet angle parameters (Eisenberg), and the helical wheel projection display for AM and PAMP (DNASTAR).

At page 12, please replace/rewrite paragraph 6 from lines 34-35 as follows:

(Amended)

Figures 28A-28D: Figures 28A-28D set forth the growth effects of AM. A representative human tumor cell line,

At page 13, please replace/rewrite paragraph 2 under "DETAILED DESCRIPTION OF THE INVENTION" from lines 18-19, as follows:

(Amended)

Specifically, the present invention relates to the following novel isolated AM peptide and oligonucleotide sequences:

At page 15, please replace/rewrite paragraph 3, lines 30, as follows:

(Amended)

To characterize the functions of AM in normal tissues, the distribution of AM was studied in normal and malignant lung using immunocytochemical techniques to localize the peptide, and *in situ* reverse transcriptase-polymerase chain reaction (RT-PCR) to study the expression of its messenger RNA (mRNA) in formalin-fixed paraffin-embedded specimens.

IN THE CLAIMS:

Canceled Claims:

Please cancel replacement claims 1-43 of the parent application without prejudice or disclaimer.

New Claims:

Please add new claims 44-70 as follows:

44. (New) An isolated adrenomedullin peptide selected from the group consisting of PO70 (SEQ ID NO: 1), PO71 (SEQ ID NO: 2) and PO72 (SEQ ID NO: 3) .

45. (New) An antibody reactive with at least one of the peptides of claim 44.

46. (New) Use of the antibody of claim 45 in the treatment of a patient suffering from a cancer or tumor, comprising contacting cancer or tumor cells with an amount of said antibody effective to prevent or treat the cancer or tumor.

47. (New) Use according to claim 46 wherein the cancer or tumor cells are selected from the group consisting of adrenal, nervous system, lung, colon, ovarian, prostate, chondrosarcoma, pancreas, or breast.

48. (New) A method for diagnosing or monitoring a disease other than hypotension, hypertension or cardiac incompetence, comprising measuring the levels of adrenomedullin in a sample, wherein the presence or absence of adrenomedullin indicates the existence of, or predisposition to, the disease.

49. (New) The method of claim 48, wherein the disease is diabetes, renal disease, bone disease, skin disease, or hematopoietic cell disease.

50. (New) Use of the adrenomedullin peptides of claim 44 or antibodies reactive therewith for the treatment of a patient suffering from type II diabetes, comprising providing to the patient an amount of said peptides

or antibodies effective to regulate insulin secretion and blood glucose metabolism.

51. (New) Use of the adrenomedullin peptides of claim 44 or antibodies reactive therewith for use in diagnosing or treating women for conditions related to pregnancy.

52. (New) Use according to claim 51 wherein the condition is preeclampsia or fetal growth.

53. (New) Use of the adrenomedullin peptides of claim 44 or antibodies reactive therewith for use in regulating neuronal activity in areas of the central nervous system, comprising administering to a subject said peptides or antibodies in an amount effective to regulate neurotransmission or neuron growth.

54. (New) Use of the adrenomedullin antibody of claim 45 for regulating, lessening, or inhibiting an allergic or inflammatory response due to the degranulation of mast cells or involvement of immune response cells, comprising administering said antibodies in an amount effective to lessen or inhibit the degranulation of mast cells.

55. (New) Use of the adrenomedullin peptides of claim 44 or antibodies reactive therewith for treating bacterial or fungal infections, comprising administering to a subject said peptides or antibodies in an amount effective to inhibit or prevent bacterial or fungal growth.

56. (New) Use of the adrenomedullin peptides of claim 44 for facilitating the repair or healing of chafed skin, skin lesions, wounds, and surgical incisions, comprising

applying said adrenomedullin peptides to the surface of the skin of a subject in an amount effective to facilitate the repair or healing.

57. (New) Use of the adrenomedullin peptides of claim 44 or antibodies reactive therewith in promoting organ and bone development.

58. (New) A pharmaceutical composition comprising the adrenomedullin peptides of claim 44.

59. (New) A pharmaceutical composition comprising the adrenomedullin antibodies of claim 45.

60. (New) Use of isolated adrenomedullin peptide PAMP-20 (SEQ ID NO: 7) or antibodies reactive therewith for the treatment of a patient suffering from a cancer or tumor, comprising contacting cancer or tumor cells with an amount of said peptide or antibodies effective to prevent or treat the cancer or tumor.

61. (New) Use according to claim 60 wherein the cancerous cells are selected from the group consisting of adrenal, nervous system, lung, colon, ovarian, prostate, chondrosarcoma, pancreas, or breast.

62. (New) Use of isolated adrenomedullin peptide PAMP-20 (SEQ ID NO: 7) or antibodies reactive therewith for the treatment of a patient suffering from type II diabetes, comprising providing to the patient an amount of said peptides or antibodies effective to regulate insulin secretion and blood glucose metabolism.

63. (New) Use of isolated adrenomedullin peptide PAMP-20 (SEQ ID NO: 7) or antibodies reactive therewith in diagnosing or treating women for conditions related to pregnancy.

64. (New) Use according to claim 63 wherein the condition is preeclampsia or fetal growth.

65. (New) Use of isolated adrenomedullin peptide PAMP-20 (SEQ ID NO: 7) or antibodies reactive therewith for regulating neuronal activity in areas of the central nervous system, comprising administering to a subject said peptide or antibodies in an amount effective to regulate neurotransmission or neuron growth.

66. (New) Use of antibodies reactive with isolated adrenomedullin peptide PAMP-20 (SEQ ID NO: 7) for regulating, lessening, or inhibiting the allergic response due to the degranulation of mast cells, comprising administering said antibodies in an amount effective to lessen or inhibit the degranulation of mast cells.

67. (New) Use of isolated adrenomedullin peptide PAMP-20 (SEQ ID NO: 7) or antibodies reactive therewith for treating bacterial or fungal infections, comprising administering to a subject said peptide or antibodies in an amount effective to inhibit or prevent bacterial or fungal growth.

68. (New) Use of isolated adrenomedullin peptide PAMP-20 (SEQ ID NO: 7) for facilitating the repair or healing of chafed skin, skin lesions, wounds, and surgical incisions, comprising applying said adrenomedullin peptides to the surface of the skin of a subject in an amount effective to facilitate the repair or healing.

69. (New) Use of isolated adrenomedullin peptide PAMP-20 (SEQ ID NO: 7) or antibodies reactive therewith for promoting organ and bone development.

70. (New) An isolated adrenomedullin oligonucleotide selected from the group consisting of AM_{94-114} (SEQ ID NO: 4), $AM_{444-464}$ (SEQ ID NO: 5) and $AM_{289-309}$ (SEQ ID NO: 6).

REMARKS

In this Preliminary Amendment, pages 3, 8, 12, 13 and 15 of the specification have been amended. A marked up copy of the replacement/rewritten paragraphs of the specification as specified above is provided herewith on pages 10-12. The line numbers herein refer to the line numbers of the published PCT application no. WO 97/07214 (PCT/US96/13286). Claims 1-43 have been canceled without prejudice; new claims 44-70 have been added to remove redundancies among the claims in the parent application. The new claims are fully supported by the previous claims.

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AUTHORIZATION

Should any additional fees be deemed to be properly assessable in this application, the Commissioner is hereby authorized to charge Deposit Account No. 13-4500, Order No. 2026-4202US4. **A duplicate copy of this sheet is attached.**

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Date: August 16, 2000

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Replacement Paragraphs of the Specification – Marked up Copy

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